TABLE I

IONIZATION CONSTANTS FOR PIPERAZINE AND DERIVATIVES (t = 25°c.)

No.	Compound	pK_1	pK_2	$K_1{}^a$	$K_2{}^b$
1	Piperazine	3.97	8.34	1.07×10^{-4}	3.6×10^{-9}
2	2-Methylpiperazine	4.10	8.54	8.0×10^{-5}	2.9×10^{-9}
3	2,5-Dimethylpiperazine (*cis*)	4.02	8.77	9.5×10^{-5}	1.7×10^{-9}
4	2,5-Dimethylpiperazine (*trans*)	4.16	8.66	6.9×10^{-5}	2.2×10^{-9}
5	2,6-Dimethylpiperazine	4.14	8.60	7.2×10^{-5}	2.5×10^{-9}
6	1,2,4-Trimethylpiperazine	5.64	10.06	2.3×10^{-6}	8.6×10^{-11}
7	1,4-Bis(2-hydroxypropyl)-2-methylpiperazine	5.85	10.37	1.4×10^{-6}	4.3×10^{-11}
8	1,4-Bis(3-dimethylaminopropyl)-*trans*-2,5-dimethylpiperazine[c]	4.57	4.57	2.7×10^{-5}	2.7×10^{-5}
9	2,3,5,6-Tetramethylpiperazine	4.06	8.89	8.7×10^{-5}	1.3×10^{-9}

[a] ionic strength, $\mu = 2.5 \times 10^{-2}$. [b] ionic strength, $\mu = 7.5 \times 10^{-2}$. [c] $K_3 = 2.1 \times 10^{-1}$; $pK_3 = 8.68$; ionic strength, $\mu = 1.3 \times 10^{-1}$.

and some of its derivatives. Classical concentration constants were calculated for a specified ionic strength.

EXPERIMENTAL

The purity of the amines selected for these studies was determined by titration, and assayed 98 ± 2% in all cases on a dry weight basis. Where the amines were dibasic the two titration breaks were equal. Purity was further substantiated by boiling point or melting point data, and gas chromatography.

About 0.005 mole of amine was dissolved in 100 ml. of distilled water and titrated with 0.5N hydrochloric acid. Potentiometric titrations were performed at 25°. The electrode system was standardized before and after each titration using pH 4.00, 7.00, and 10.00 reference buffers. The activity coefficient of Kortüm and Bockris was used to calculate hydroxide ion concentration.[1] At least two titrations meeting all the specified conditions were performed for each amine. The results are summarized in Table I.

DISCUSSION

All pK values for the bases considered were calculated for the buffer region where effect of impurities is slight. Maximum deviation from the average pK values was ± 0.05 pK units. Average deviation was ± 0.03 pK units.

The values in Table I show that the addition of one to four methyl groups in the 2,3,5 and/or 6 ring positions decreases the basicity of the amine only slightly. However substitution in the 1,4 position, so that the amine is changed from a secondary amine to a tertiary amine, causes a larger decrease in basicity. In the case of 1,4-bis(3-dimethylaminopropyl)-*trans*-2,5-dimethylpiperazine both side chain amine nitrogens titrate in water as one end point. Only one of the ring nitrogens is titrated, and this nitrogen is a very weak base. Comparison of compounds number 6, and 7 suggests that the 2-hydroxypropyl group is a stronger electron attracting group than the methyl group, thereby reducing the electron density of the amine nitrogen and rendering it less basic. In summary, the basicity of the piperazine nitrogen decreases with methyl substitution of the ring hydrogens, and the decrease in basicity is greater for disubstitution and greatest for trisubstitution.

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[1] G. Kortüm and J. O'M. Bockris, *Textbook of Electrochemistry*, 2nd ed., Vol. II, Elsevier Publishing Co., N. Y., 1951, p. 681.

Oxidation of Hindered Phenols. IX. Equilibria between Phenoxy Radicals

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In 1926 Conant suggested[1] that a hydrogen atom may be reversibly removed from a phenolic hydroxyl group. This suggestion, which formed part of the basis for Conant's apparent oxidation potential scale, seems eminently reasonable, and has received support from Fieser's measurements of critical oxidation potentials[2] and recently through molecular orbital calculations.[3] During our work on stable phenoxy radicals, equilibria between such radicals and their parent phenols have frequently been observed.[4]

Thus, if a small amount of 2,6-di-*t*-butyl-4-*t*-butyoxyphenol is added to a solution of the blue 2,4,6-tri-*t*-butylphenoxy (I), the red color of 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy (II) immediately appears. On addition of 2,4,6-tri-*t*-butylphenol to this solution the color changes to purple and, if enough of the tri-*t*-butylphenol is added, goes back to blue. Obviously, a mobile equilibrium exists; hence, we undertook the evaluation of the equilibrium constant. Since a relatively large number of

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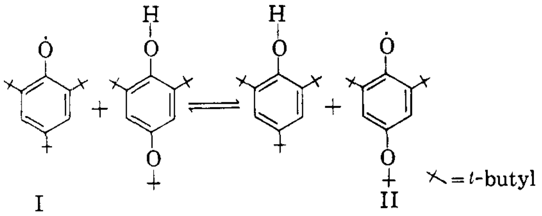
[1] J. B. Conant and M. Pratt, *J. Am. Chem. Soc.*, **48**, 3220 (1926).

[2] L. F. Fieser, *J. Am. Chem. Soc.*, **52**, 5204 (1930).

[3] N. Hush, *J. Chem. Soc.*, 2375 (1953).

[4] See C. D. Cook, D. A. Kuhn, and P. Fianu, *J. Am. Chem. Soc.*, **78**, 2002 (1956).



I II

2,6-di-*t*-butyl-4 substituted phenols now exist which give stable phenoxy radicals (among them 4-phenyl,4-cyano,4-triphenylmethyl[5] and 4-benzoyl[5]) we hoped that by establishing a series of equilibria we would develop a graduated series of oxidants of essentially constant steric requirements which might be of considerable utility in the study of oxidations in nonaqueous systems. Qualitative studies with diphenoquinone had previously shown that 2,6,di-*t*-butyl-4-methoxyphenoxy, the poorest oxidant of the group, has an apparent oxidation potential in the order of .95 to 1 volt.[4] Finally, it is easily shown that a rough but significant correlation exists between Hammett σ values and Fieser's critical oxidation potentials. The slope of such a correlation suggests that our projected series would provide a relatively wide range of oxidation potentials.

Unfortunately, the experimental difficulties encountered in the study of these equilibria were too great to warrant continuation of the project. This note is a report of the results on the one equilibrium which was studied in considerable detail, that between 2,4,6-tri-*t*-butylphenoxy and 2,6-di-*t*-butyl-4-*t*-butoxyphenol.

The equilibriun was followed spectrophotometrically, I having a broad absorption maximum at 625 mμ, and II having a rather intense minimum at 445 mμ. Tri-*t*-butylphenoxy (I) was conveniently generated quantitatively by the reaction of mercury with 2,4,6-tri-*t*-butyl-4-bromocyclohexa-2,5-diene-1-one[6] in an evacuated system. Known solutions of the radical in benzene were added, under vacuum, to mixtures of the two phenols to establish the equilibria.

The results are shown in Fig. 1 which can be summarized in the form $\log K = \dfrac{0.7464}{T} - 0.7890$. The equilibrium constant for Eq. 1 as written is 51.7 ± 4.1 at 25°, and the enthalpy change is -3.42 ± 0.17 kcal/mole.

Two runs on 2,6-di-*t*-butyl-4-methoxyphenol with 2,4,6-tri-*t*-butylphenoxy gave approximately 210 as the equilibrium constant at 25° and approximately -5 kcal/mole as the enthalpy change. While no great precision can be attached to these latter figures, they would seem to be of the right order of magnitude as compared to those for the reaction with the *t*-butoxy compound; the methoxy group tends to increase the electron density around the phenolic hydroxyl more than the *t*-butoxy group and hence the *p*-methoxy phenol should be the more readily oxidized.

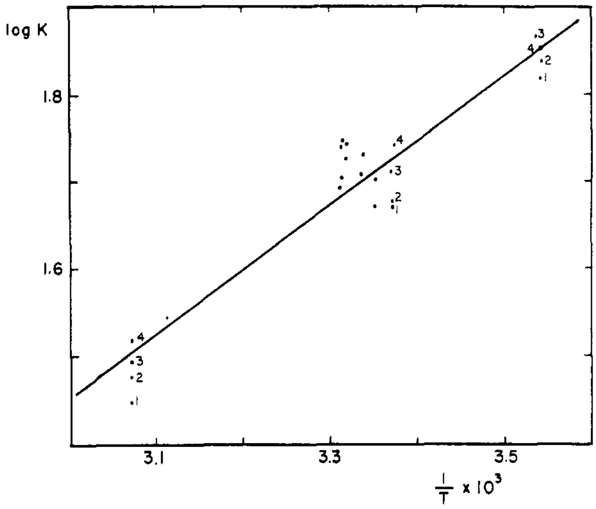


Fig. 1. van't Hoff plot for the equilibrium between 2,4,6-tri-t-butylphenoxy and 2,6-di-t-butyl-4-butoxyphenol

EXPERIMENTAL

A. Determination of absorbency index of 2,4,6-tri-t-butylphenoxy (I). The absorbency index of tri-*t*-butylphenoxy was determined in the apparatus shown in Fig. 2. A known solution of the bromocyclohexadienone in benzene was added to the flask which contained several glass beads. The solution was degassed by alternate freezing and thawing and was then sealed off under vacuum at constriction *A*.

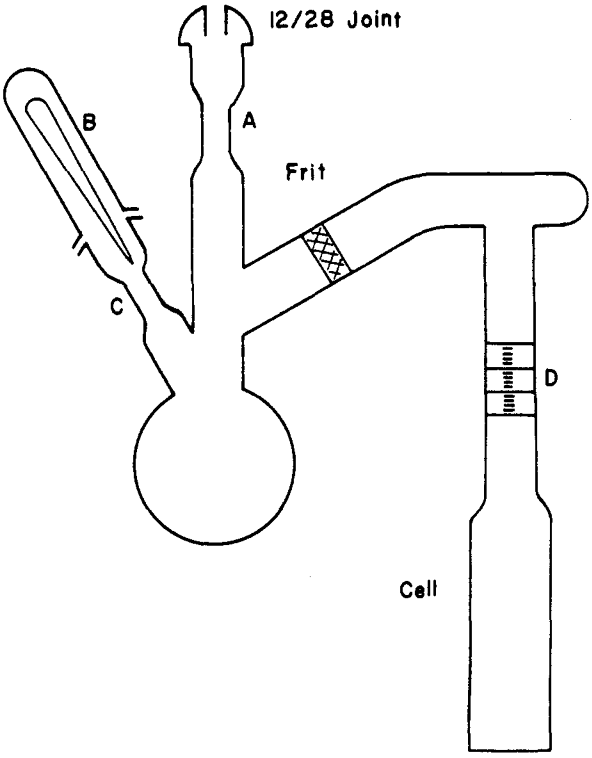


Fig. 2. Apparatus for the determination of the absorbency index of 2,4,6-tri-t-butylphenoxy

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(5) C. D. Cook and N. Gilmour, unpublished work.

(6) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

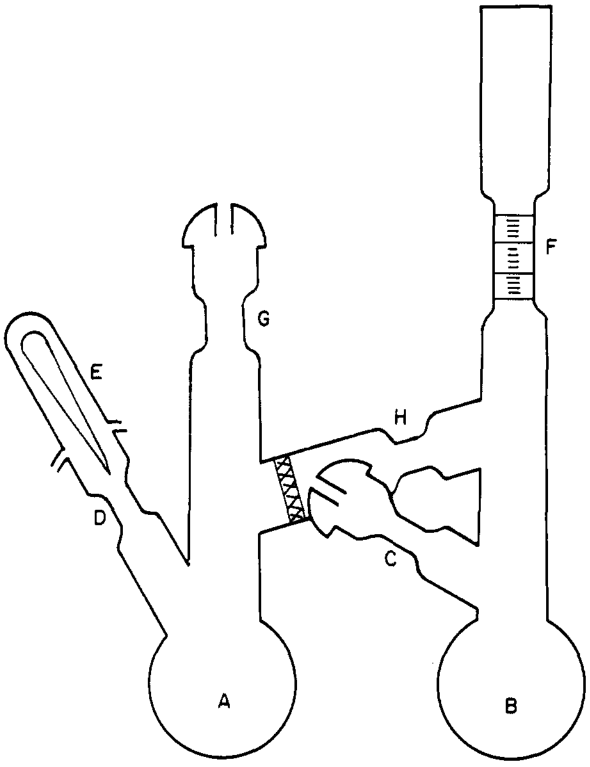

Fig. 3. Apparatus used for measuring the absorbency index of 2,6-di-t-butyl-4-butyoxyphenoxy and for studying the equilibrium

While still frozen, assembly *B* was rotated to break the enclosed ampule containing approximately one ml. of mercury. Constriction *C* was then sealed and the apparatus placed in a mechanical shaker. At the end of the shaking period (*ca.* 2 hr.) the blue solution was filtered through the medium grade frit. By cooling the bulb, benzene was distilled back into the reaction flask and used to rinse the bulb and frit. When rinsing was completed, the volume was determined from the calibrations at *D*, and the absorbency measured in a Beckman DU Spectrophotometer. The absorbency index at 625 $m\mu$ was found to be 400 ± 3; at 445 $m\mu$, 11 ± 3. The result at 625 $m\mu$ agrees very well with a value of 410 ± 8 obtained by an entirely different technique.[7] At room temperature, the radical solutions proved to be very stable, losing about 1% of their absorbency on standing 24 hr.

B. Determination of the absorbency indices of 2,6-di-t-butyl-4-t-butyoxyphenoxy and of 2,6-di-t-butyl-4-methoxyphenoxy and the equilibrium constants. For these determinations, the apparatus shown in Fig. 3 was used. A five- to sixfold excess of the alkoxyphenol in low boiling petroleum ether (carefully purified) was added to bulb *B*, and the ether removed by suction applied to the ball joint at *C*. The constriction at *C* was then sealed off at the torch and 2,4,6-tri-*t*-butylphenoxy generated in flask *A* as described under part A. The phenoxy radical was filtered thru the frit into *B* and after several rinsings, the solution was frozen and the apparatus sealed off at *H*. The absorbency of the resultant red solution was then measured at 625 $m\mu$ and at 445 $m\mu$. Since there was a large excess of alkoxyphenol, the equilibrium (Eq. 1) was displaced far to the right, and from the absorbency measurements and the volume it was possible to directly calculate approximate extinction coefficients for the alkoxyphenoxy radicals. These were applied to the equilibrium data (see below) to calculate approximate equilibrium constants. The constants were then used to correct the total absorbency for the small amounts of tri-*t*-butylphenoxy radical present in the system. As these corrections were on the order of only 3%, the method was considered highly satisfactory. At 625 $m\mu$, 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy had an absorbency index of 58.2 ± 2.7; at 445 $m\mu$ 105.9 ± 3.7; 2,6-di-*t*-butyl-4-methoxyphenoxy gave 31.2 ± 3 at 625 $m\mu$ and 89.5 ± 3.4 at 445 $m\mu$.

For the equilibrium constant runs, appropriate known mixtures of the two phenols were added to bulb *B*, solutions of 2,4,6-tri-*t*-butylphenoxy then added from bulb *A*, and the apparatus sealed at *H* after freezing. From the absorbencies at 625 $m\mu$ and 445 $m\mu$ it was then possible to calculate the concentration of each species in the equilibrium mixture. During these reactions small decreases in radical concentration were noted; the total radical concentration can be calculated both from the spectral data and from the amount of bromocyclohexadienone used at the start. The former gave results averaging 4% less than the latter. This small loss was not sufficiently consistent to be some constant error in technique, and was most probably due to small amounts of the bromocyclohexadienone entering the frit and not reacting with the mercury. (Unlike the situation in part A, it is impossible in this case to return the materials to flask *A* and reshake to ensure complete reaction.)[8] The equilibrium constants did not vary in any regular way with the size of the loss, and it was therefore presumed that they did not introduce any major error.

All spectral measurements were made after the samples had equilibrated at the appropriate temperature in a constant temperature cabinet mounted on top of the spectrometer cell compartment. Little, if any, loss of radical occurred, during a run; it was found that the equilibrium mixtures averaged a loss of 2.4% per day in radical concentration on standing at room temperature.

Numerous runs were made at 25° to ensure that the technique worked and then four runs were carried over the full temperature range. These four runs are numbered on Fig. 1. Had the plot been confined to these runs, the van't Hoff isotherm would have been a bit lower but would have given essentially the same value for the enthalpy change.

Although solutions of 2,6-di-*t*-butyl-4-methoxyphenoxy gave good results on extinction coefficient measurements, attempts to measure its equilibrium constant on reaction with tri-*t*-butylphenol were generally frustrated due to the instability of the solutions. This was apparently due to some extraneous factor since two runs gave satisfactorily stable solutions. From them we estimate the equilibrium constant (written in the same direction as Eq. 1) to be on the order of 210 at 25° and ΔH to about -5 kcal/mole.

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[7] C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, 81, 1176 (1959).

[8] The bromocyclohexadienone has been shown to rapidly interact with the alkoxy phenols; probably a bromine atom is transferred followed by decomposition of the alkoxybromocyclohexadienone to yield 2,6-di-*t*-butylquinone. Direct attempts to brominate either of these two alkoxy phenols lead to such a result.

Identification of Neophytadiene in Burley Tobacco and in Cigarette Smoke[1]

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During the investigation of the hydrocarbons in aged burley tobacco, a pentane extract was